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Health and Environmental Effects Profile for Dimethyl Terephthalate

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DIMETHYL TEREPHTHALATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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16. ABSTRACT

The Health and Environmental Effects Profile for dimethyl terephthalate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Dimethyl terephthalate has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for dimethyl terephthalate is 1.3×10^{-1} (mg/kg bw/day) for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
GC	Gas chromatography
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

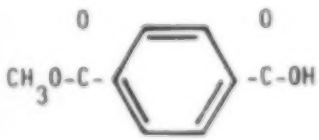
Dimethyl terephthalate is the common name for the dimethyl ester of 1,4-benzenedicarboxylic acid. The structure of dimethyl terepnthalate is given below:

Molecular formula: $C_{10}H_{10}O_4$

Molecular weight: 194.19

The Chemical Abstracts Service (CAS) Registry Number for dimethyl terephthalate is 120-61-6.

Methyl terephthalate is the common name for the monomethyl ester of 1,4-benzenedicarboxylic acid. The structure of methyl terephthalate is given below:



Molecular formula: $C_9H_8O_4$

Molecular weight: 180.16

The Chemical Abstracts Service (CAS) Registry Number for methyl terephthalate is 1679-64-7.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Dimethyl terephthalate is a white crystalline solid at room temperature. It undergoes the characteristic chemical reactions of dicarboxylic acid esters. Some of its physical properties are given below (SRC, 1979):

Boiling Point:	(sublimes)
Melting Point:	141.0-141.8°C
Vapor Pressure:	1 mm Hg at 100°C
Water Solubility:	insoluble at 25°C
Specific Gravity:	1.194 (20/4°C)

Data regarding the physical properties of methyl terephthalate were not located in the available literature.

1.3. PRODUCTION DATA

Dimethyl terephthalate is currently produced by three manufacturers. E.I. duPont produces 550 and 1250 million pounds/year at their Old Hickory, TN, and Wilmington, NC, plants, respectively. Eastman Kodak produces 550 million pounds/year at each of their plants, which are located in Columbia, SC, and Kingsport, TN. Hercofina produces 1300 million pounds/year at Wilmington, SC (SRI, 1983). It is manufactured by oxidizing p-xylene to methyl terephthalate, followed by esterification with methyl alcohol (Frey and Soder, 1975).

No information regarding the current production of methyl terephthalate, other than its production as an intermediate in the synthesis of dimethyl terephthalate, was located in the available literature. The 1977 TSCA production file lists two producers of methyl terephthalate, but does not report production volumes. The producers were duPont, Wilmington, NC, and Old Hickory, TN and Hercofina, Wilmington, NC (U.S. EPA, 1977).

1.4. USE DATA

Dimethyl terephthalate and purified terephthalic acid are used interchangeably as monomers in the production of polyethylene terephthalate. In

1981 and 1982, the combined demand for dimethyl terephthalate and terephthalic acid was 6.4 and 6.1 billion pounds, respectively (CMR, 1982). Dimethyl terephthalate and terephthalic acid are used to produce the following products (CMR, 1982):

Polyethylene terephthalate (polyester) fibers	82%
Polyethylene terephthalate film	8%
Polyethylene terephthalate bottle resin	6%
Miscellaneous (including polybutane terephthalate)	4%

Dimethyl terephthalate has also been used as a dye carrier (Wannemacher and DeMaria, 1979).

duPont produces a thermoplastic polyester elastomer called Hytrel, which is derived from polytetrahydrofuran 1,4-butanediol and methyl terephthalate (Dreyfuss and Dreyfuss, 1982).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Few data exist regarding the fate of dimethyl terephthalate in air, soil and water. It is generally processed in the molten state in closed systems, and any airborne emissions may consist primarily of dust or fume. Dimethyl terephthalate can probably also enter the environment via processing plant effluent, as it has been detected in river water in the vicinity of chemical plants (Sheldon and Hites, 1978). Methyl terephthalate is a captive intermediate in the production of dimethyl terephthalate, and is also processed in the molten state. No data exist regarding the fate and transport of methyl terephthalate.

In the atmosphere, dimethyl terephthalate is reactive toward OH• radicals with a half-life of ~3 days, and is unreactive toward ozone (Brown et al., 1975).

Dimethyl terephthalate is unreactive toward RO_2• (alkylperoxy radicals) in aqueous media (Brown et al., 1975). The hydrolytic half-life of dimethyl terephthalate in neutral water at 25°C is 321 days; hydrolysis is expected to be more rapid at high pH than at neutral or low pH (Mabey and Mill, 1978).

The log octanol/water partition coefficient (K_{ow}) for dimethyl terephthalate is calculated to be 2.81 (from the toluene/water partition coefficient using the solvent regression equations of Hansch and Leo, 1979). The log sediment organic content/water partition coefficient (K_{oc}) calculated from this is 2.49 (Mabey et al., 1981). Kenaga (1980) reported that compounds having log K_{oc} values >3 are expected to sorb strongly, while those having values <2 are expected to be highly mobile. The value for dimethyl terephthalate suggests that some sorption will occur but only to a limited extent. The log bioconcentration factor (BCF), also calculated

by the method of Kenaga (1980), is 1.21 and suggests thai bioconcentration will not be significant (compounds having values >3 will concentrate significantly). No information that would enable the calculation of K_{ow}, K_{oc} or BCF values for methyl terephthalate was found in the available literature. However, since methyl terephthalate has a hydrophilic group (-COOH) which dimethyl terephthalate does not contain, the log K_{ow}, log K_{oc} and log BCF values for methyl terephthalate will be lower than those for dimethyl terephthalate. Consequently, methyl terephthalate is expected to sorb and bioconcentrate less than dimethyl terephthalate.

In situ hydrolysis of dimethyl terephthalate in soils is dependent upon pH. Hydrolysis may be rapid in alkaline soil, but in neutral and acidic soil the hydrolysis may be slow (Brown et al., 1975). Kurane et al. (1977) investigated the biodegradability of several phthalate esters by the bacterium, Pseudomonas acidovorans 256-I. This strain was isolated from soil and wastewater, and was observed to degrade dioctyl phthalate to a greater extent than 24 other strains in a screening test. When aerobically cultured in media containing dimethyl terephthalate as the sole carbon source, no degradation was observed after 40 day incubation at 30°C. This study is not a sufficient basis for predicting whether dimethyl terephthalate will be biodegraded in the environment.

3. EXPOSURE

Dimethyl terephthalate was detected in the Delaware River (between Wilmington, DE, and Trenton, NJ; exact location not stated) at a concentration of 0.06 ppb (Sheldon and Hites, 1978).

Hughes et al. (1979) measured the fugitive hydrocarbon emissions from seals on pumps, valves, relief valves, agitators and flanges in petrochemical plants. Using the emission rates as measured by a flame ionization detector (FID), the average mass of fugitive emissions from petrochemical plants manufacturing dimethyl terephthalate was estimated to be 10.6 metric tons/year from sources other than the valves and flanges; data for emissions from valves and flanges were incomplete.

Soft drink bottles, food packaging films and polyester fibers made from co-polymerized dimethyl terephthalate and ethylene are used at ever increasing rates (CMR, 1982). Whether residual monomer or biochemical degradation products are released from these finished polymers and result in significant exposure to humans has not been ascertained at this time.

4. COMPOUND DISPOSITION AND PHARMACOKINETICS

Pertinent data regarding the disposition and pharmacokinetics of methyl terephthalate were not found in the available literature.

4.1. ABSORPTION

Moffitt et al. (1975), on the basis of excretion studies, concluded that dimethyl terephthalate was rapidly absorbed regardless of the dose by the dermal, oral and inhalation routes in rats upon single or repeated administration. At least 65% of the radioactivity contained in a single dose of uniformly ring-labeled ^{14}C-dimethyl terephthalate was excreted in the urine of CR rats within 24 hours and over 70% was excreted in the urine by 48 hours after administration by gavage. These results were obtained over a range of dose levels from trace amounts through 40 mg; similar results were obtained with repeated oral administration (5 doses during 10 days). Experimental details are provided in Section 4.4. In similar studies by Moffitt et al. (1975), rats were given ^{14}C-dimethyl terephthalate by dermal application or intratracheal administration; however, absorption by these routes was less efficient than by the oral route. Approximately 10% of the total single or repeated dermal dose of radioactivity was excreted in the urine and ~2% was excreted in the feces during the 10 days the compound was in contact with the skin. In the intratracheal experiments, 52% of the dose was excreted in the urine within 24 hours and 58% was excreted in the urine within 48 hours of administration of a single dose. An additional 3% was excreted in the feces within 48 hours. Similar results were obtained with repeated intratracheal administration (5 doses during 10 days). Experimental details are provided in Section 4.4. The vehicle for the oral studies was peanut oil; however, the vehicle for the dermal and intratracheal studies was 1% Triton X-100 in distilled water.

In an unpublished study (duPont, 1979), a diet containing 5% dimethyl terephthalate was given to rats for 5 days The compound was "almost completely" absorbed based on the observed recovery of the compound and its metabolites in the urine.

4.2. DISTRIBUTION

Moffitt et al. (1975) gave male CR rats repeated (every other day for 5 doses in 10 days) doses of uniformly ring-labeled ^{14}C-dimethyl terephthalate by gavage as described in Section 4.4., and assayed their organs for radioactivity on day 10, 24 hours after administration of the last dose. The radioactivity found in the blood, liver, lung, heart, kidney, spleen, adrenals, pancreas, testes and brain accounted for <0.1% of the total dose, regardless of its amount. Repeated administration of the compound by intratracheal instillation and dermal application gave similar results. In addition, with intratracheal administration, <1% of the dose of radioactivity was found in the lungs and tracheal lymph nodes. The compound apparently is not retained in the tissues of rats under these experimental conditions.

D'A Heck and Kluwe (1980) observed "only trace levels" of radioactivity in the carcasses of 3 rats killed 48 hours after the gavage administration of a single dose of 63 µCi ring-labeled ^{14}C-dimethyl terephthalate (specific activity not reported).

4.3. METABOLISM

Dimethyl terephthalate is metabolized primarily to its corresponding acid in rats, with only traces excreted unchanged in the urine (Workplace Environmental Exposure Level Guide, 1982). This is supported by the observations of D'A Heck and Kluwe (1980) who studied the metabolism of a single dose of ring-labeled ^{14}C-dimethyl terephthalate administered to rats by

gavage as described previously (see Section 4.2.). Only a single radioactive peak (corresponding to ^{14}C-terephthalic acid) was observed in the high pressure liquid chromatograms of the urine collected from rats for 24 hours after treatment with ^{14}C-dimethyl terephthalate. The feces of these rats were collected for 24 hours, and were found to contain only trace levels of radio-labeled monomethyl terephthalate, dimethyl terephthalate and terephthalic acid. Terephthalic acid was detected in the urine of rats given diets containing 1 or 2% dimethyl terephthalate.

Moffitt et al. (1975) observed that most of the radioactive label excreted in the urine and feces of rats treated with uniformly ring-labeled ^{14}C-dimethyl terephthalate was in the water soluble fraction.

4.4. EXCRETION

Moffitt et al. (1975) studied the excretion of uniformly ring-labeled ^{14}C-dimethyl terephthalate following single and repeated oral, intratracheal and dermal administration in male Charles River rats.

Groups of 5 rats received single or repeated (5 doses over 10 days, alternate days) doses of 4 μCi ^{14}C-dimethyl terephthalate (specific activity not reported) along with 0, 20 or 40 mg of unlabeled dimethyl terephthalate in peanut oil by gavage (Moffitt et al., 1975). The urine and feces were collected, and the repeated-dose animals were killed on day 10 of the experiment, at which time their organs were assayed for radioactivity (see Section 4.2.). In the single-dose experiments, more than 80% of the administered radioactivity was excreted in the urine and feces within 48 hours of administration; >90% of this excreted radioactivity was found in the urine. In the repeated-dose experiments, more than 89% of the administered radioactivity was found in the urine and feces within 24 hours of the last administration; ~85% of this excreted radio-activity was found in

the urine. A linear correlation between urinary and fecal excretion and time and dosage was observed with repeated administration.

Groups of 5 rats received single or repeated (5 doses over 10 days, alternate days) doses of 6 μCi ^{14}C-dimethyl terephthalate (specific activity not reported) along with 0, 5 or 10 mg unlabeled compound in aqueous Triton X-100 emulsions by intratracheal injection (Moffitt et al., 1975). The urine and feces were collected, and the repeated-dose animals were killed on day 10 of the experiment, at which time their organs were assayed for radioactivity (see Section 4.2.). Poor total recoveries of radioactivity from the two higher doses were observed. This was attributed to inadequate suspension of the compound before administration or reflex expulsion of a portion of the doses. Of the radioactivity excreted, however, most (~94%) was found in the urine 24 hours after single or repeated administration.

Groups of 5 rats received single or repeated (5 doses over 10 days, alternate days) doses of 80 mg of uniformly ring-labeled ^{14}C-dimethyl terephthalate (4 μCi) in aqueous Triton X-100 emulsions to their shaved backs. In both the single dose and repeated dose studies, a gauze patch was used to cover the dosed (1 in.^{2}) area for 10 days, and was removed only to allow repeated dosing (Moffitt et al., 1975). The urine and feces were collected during the entire 10 days, and the animals were killed on day 10 of the experiment, at which time their organs were assayed for radioactivity (see Section 4.2.). Approximately 56, 11 and 26% of the recovered radioactivity was found in the urine, feces and application area.

D'A Heck and Kluwe (1980) reported that only one metabolite, terephthalic acid, was observed in the urine of rats orally treated with dimethyl terephthalate by gavage or dietary inclusion. Further, only "trace

amounts" of radiolabeled monomethyl terephthalate, dimethyl terephthalate and terephthalic acid were detected in the feces of rats treated with ring-labeled ^{14}C-dimethyl terephthalate up to 24 hours after administration.

The experiments of Moffitt et al. (1975) and D'A Heck and Kluwe (1980) demonstrate that regardless of the route of administration dimethyl terephthalate is absorbed rapidly and excreted by the kidney, and does not accumulate in the tissues under the conditions of these studies.

5. EFFECTS

Pertinent data regarding the effects of methyl terephthalate on biologic systems were not found in the available literature.

5.1. CARCINOGENICITY

Equivocal evidence of dimethyl terephthalate's carcinogenicity in rodents was reported by the National Cancer Institute (NCI, 1979). Groups of 50 male and 50 female F-344 rats and B6C3F$_1$ mice were fed diets containing 0, 2500 or 5000 ppm dimethyl terephthalate for 103 weeks. Body weights, food consumption and evidence of clinical signs were monitored. Two weeks after the test diet was discontinued, the animals were necropsied, and major tissues, organs and gross lesions underwent gross and microscopic evaluation.

A variety of tumors normally found in aging F-344 rats was observed in all groups including controls and could not be attributed to the administration of dimethyl terephthalate. The incidence of alveolar/bronchiolar carcinomas in male mice was 1/49 in matched controls, 1/49 in the low dose group and 6/49 in the high dose group. The incidence of alveolar/bronchiolar adenomas or carcinomas in male mice was 1/49 in matched controls, 8/49 in the low-dose group and 13/49 in the high-dose group. The incidence of malignant lymphomas in female mice was 16/48 in matched controls, 5/50 in the low-dose group and 27/49 in the high-dose group. On initial examination, these data appear to demonstrate the carcinogenicity of dimethyl terephthalate by oral administration. The incidence of lymphomas in B6C3F$_1$ female mice and alveolar/bronchiolar adenomas and carcinomas in B6C3F$_1$ male mice, however, is quite variable. Groups of male B6C3F$_1$ control mice occupying the same room as mice in this study had higher incidences of alveolar/bronchiolar adenomas and carcinomas (e.g., 5/49, 6/46, 9/49) than the matched control groups. Using these rates of tumor

induction, the incidence of alveolar/bronchiolar adenomas and carcinomas in treated males is not significantly different from controls. The NCI (1979) concluded that under the conditions of this study, dimethyl terephthalate was not carcinogenic for F-344 rats or B6C3F$_1$ mice.

According to Dickson (1981), an initial report of this study concluded that dimethyl terephthalate was carcinogenic to male mice; the final report (NCI, 1979) includes a reevaluation of the data, giving more weight to a comparison with pooled controls, in response to comments by a manufacturer of the chemical. IARC (1983) considered evaluating dimethyl terephthalate for carcinogenic risk, but did not do so because "adequate data on carcinogenicity were not available."

Pertinent data regarding the carcinogenicity of methyl terephthalate were not located in the available literature. It is not presently scheduled for testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

Dimethyl terephthalate was not mutagenic in an Ames assay performed in the presence or absence of metabolic activation (duPont, 1979). Details of this study were not available.

5.3. TERATOGENICITY

In an abstract of a Russian study (Krotov and Chebotar, 1972), dimethyl terephthalate ("sublethal doses") administered to pregnant rats by intraperitoneal injection or continuous inhalation resulted in maternal toxicity, but not embryotoxic or teratogenic effects.

5.4. OTHER REPRODUCTIVE EFFECTS

Krasavage et al. (1973) observed a dose-related decrease in mean body weights at weaning in offspring born to male and female rats (20/sex/dose level) fed diets containing 0.25, 0.5 or 1.0% dimethyl terephthalate. This

decrease in body weight was statistically significant, as compared with controls, in the 0.5 and 1.0% dietary groups. The males had been on the test diet for 115 days before mating, while the females were on the test diet for 6 days before mating and continuing through weaning of the offspring. Treatment did not affect the ability of the males to inseminate or the number of pregnancies, length of gestation period, litter size and mortality of offspring at birth through weaning.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

A subchronic feeding study was conducted prior to the chronic NCI carcinogenesis study to determine the maximum tolerated dosage. Groups of 10 male and 10 female F-344 rats and B6C3F$_1$ mice received diets containing 0, 1750, 2500, 5000, 10,000 or 20,000 ppm dimethyl terephthalate 7 days/week for 13 weeks. Mortality, body weights, food consumption and behavior were monitored during exposure, and histopathological evaluation was conducted when exposure was terminated. No effects on these parameters were observed that were attributable to the compound, except for diffuse hepatocellular swelling in all exposed groups of rats and mice. The hepatocellular swelling was considered to be compound related, but not dose related (NCI, 1979).

The rats and mice in the NCI (1979) carcinogenesis chronic feeding study were also examined for signs of toxicity. Mean body weights and mortality rates of rats and mice fed diets containing 2500 or 5000 ppm dimethyl terephthalate for 103 weeks were not different from controls. No differences in outward appearance and behavior were noted in groups of treated rats as compared with controls. In mice, a greater frequency of alopecia was noted among treated females and evidence of fighting was observed more frequently among treated males than among corresponding controls. Examination of the reported incidences of nonneoplastic lesions indicates that dimethyl tere-

phthalate may be associated with chronic inflammation of the kidney in male mice and female rats. The incidences of chronic kidney inflammation in male mice were 2/49 (control), 4/49 (low dose) and 11/49 (high dose). All groups of female mice had low incidences of this condition. In female rats, the incidences of chronic kidney inflammation were 3/49 (control), 5/49 (low dose) and 9/49 (high dose). All groups of male rats, including controls, had high incidences of this condition. No adverse effects on the livers of treated rats and mice were observed that were attributed to dimethyl terephthalate (NCI, 1979).

Krasavage et al. (1973) conducted a subchronic oral and inhalation toxicity study of dimethyl terephthalate in male Long Evans rats. Groups of 30 rats were given (ad lib) diets containing 0, 0.25, 0.5 or 1.0% dimethyl terephthalate (i.e., 0, 2500, 5000 or 10,000 ppm) for 96 or 125 days. Body weights, mortality, food consumption and blood chemistry were monitored during exposure. Histopathological evaluations were performed on 10 rats/group at 96 days. No differences between control and experimental groups regarding blood chemistry, mortality, histopathology or food consumption were observed. A significantly ($P<0.05$) lower mean body weight was observed in rats fed the high dose when compared with controls.

For the inhalation portion of the Krasavage study (1973), a Wright Dust Feeder was used to prepare aerosols of dimethyl terephthalate. Groups of 30 male rats were exposed to "dust clouds" containing 0, 16.5 and 86.4 mg/m^3 for 4 hours/day, 5 days/week for 58 days. Samples of the aerosols were obtained and characterized for particle size distribution. It was estimated that the particle size distributions in the high and low dose chambers were not different and ~36% of the particles were respirable (i.e., <5 μm). Based on this, the rats received average doses of 0, 0.7 and 4.0 mg dimethyl

terephthalate/kg/day. Body weights, food consumption and blood chemistry were monitored. Histopathological evaluations were performed at interim kills immediately, 6 months and 12 months after exposure. No significant toxic effects were observed regarding body weight, food consumption, blood chemistry or pathology. The high concentration caused intermittent nose rubbing, preening and blinking, while the lower concentration did not (Krasavage et al., 1973).

5.6. OTHER RELEVANT INFORMATION

Dimethyl terephthalate appears to have a low order of acute toxicity and does not cause skin irritation (Krasavage et al., 1973) or dermal hypersensitization (Moffitt et al., 1975). LD_{50} values for acute toxicity are shown in Table 5-1.

Chin et al. (1981) reported the induction of bladder stones and epithelial hyperplasia of the urinary tract in weanling F-344 rats fed diets containing 1.5, 2 or 3% dimethyl terephthalate for 2 weeks. Incidences of these effects were higher among males than among females. These effects were absent at dietary concentrations of 0.5 and 1%. The predominant constituents of the stones were terephthalic acid and calcium. Hypercalcuria and urinary acidosis occurred even at the lowest dietary level tested, 0.5% (5000 ppm) and were thought to result from the metabolism of dimethyl terephthalate to terephthalic acid. Hypercalcuria and urinary acidosis were also produced in young adult F-344 females fed 1 or 2% dimethyl terephthalate in the diet for 3 weeks (D'A Heck and Kluwe, 1980).

TABLE 5-1

Acute Toxicity of Dimethyl Terephthalate

Species	Route	LD_{50}, gm/kg	Reference
Rat	oral	>3.2	Eastman Kodak, 1976
Rat	oral	>6.5	Krasavage et al., 1973
Rat	oral	>4.4	NIOSH, 1978
Rat	i.p.	3.9	Krasavage et al., 1973
Rat	i.p.	3.2	Eastman Kodak, 1976
Mouse	oral	>3.2	Eastman Kodak, 1976
Mouse	i.p.	1.6-3.2	Eastman Kodak, 1976

6. AQUATIC TOXICITY

Pertinent data regarding the acute or chronic effects of dimethyl or methyl terephthalate on aquatic organisms, the effects of these compounds on plants, or residues in aquatic organisms were not located in the available literature. No other relevant information regarding these compounds was found in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists (ACGIH, 1980) recommends a TLV for nuisance dusts of 10 mg/m³ (for total dust) and 5 mg/m³ (for respirable dust), based on an 8-hour TWA. A recommended Workplace Environmental Exposure Level (WEEL) for dimethyl terephthalate is the same as that recommended by the ACGIH for nuisance dusts, which dimethyl terephthalate is considered to be (Workplace Environmental Exposure Level Guide, 1982).

The maximum allowable concentration (MAC) for dimethyl terephthalate in the Soviet Union is 0.1 mg/m³ (Workplace Environmental Exposure Level Guide, 1982). A Soviet permissible concentration limit for drinking water of 1.81 mg/ℓ is recommended (Prusakov, 1966).

According to the Code of Federal Regulations, containers of food products made from dimethyl terephthalate may not be used for alcoholic foods or contain >0.08 mg/in.² surface area of water (250°F) extractables, 0.02 mg/in.² surface area of n-heptane (150°F) extractables or 0.04 mg/in.² surface area of acetic acid (212°F) extractables (21 CFR 177.1660 and 57039.6).

Pertinent data regarding standards and guidelines for methyl terephthalate were not found in the available literature.

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from the toxic effects of dimethyl terephthalate or methyl terephthalate were not located in the available literature.

8. RISK ASSESSMENT

Only one animal study has been conducted to assess the carcinogenicity of dimethyl terephthalate, and its results are equivocal. Increased incidences of malignant lymphomas in female mice and alveolar/bronchiolar adenomas and carcinomas in male mice were demonstrated when compared with a matched control group, but not when compared with a larger population of controls occupying the same room (NCI, 1979). These data do not provide clear evidence to implicate dimethyl terephthalate as a carcinogen. In addition, no evidence of the mutagenicity of dimethyl terephthalate has been found in the available literature.

To evaluate the risk of dimethyl terephthalate to humans, the data from subchronic and chronic toxicity experiments will be considered. In the NCI (1979) carcinogenicity study, female rats and male mice had some evidence of toxicity after receiving diets containing 2500 or 5000 ppm dimethyl terephthalate for 103 weeks. An increase in the incidence of chronic kidney inflammation was observed in male mice (2/49 - control, 4/49 - low dose and 11/49 - high dose) and female rats (3/49 - control, 5/49 - low dose and 9/49 high dose). In the subchronic range-finding portion of this study, a compound-related (but not dose-related) histopathological alteration (i.e., diffuse hepatic cell swelling) was observed in rats and mice fed diets containing $\geq$1750 ppm dimethyl terephthalate for 91 days; however, no such effect was reported in rats or mice given diets containing 2500 or 5000 ppm for 103 weeks. D'A Heck and Kluwe (1980) reported that hypercalcuria and urinary acidosis were produced in weanling F-344 rats by dietary levels of dimethyl terephthalate as low as 5000 ppm, fed for 2 weeks. The adverse effects on the kidney upon chronic dietary administration of dimethyl terephthalate (NCI, 1979) are consistent with the proposed metabolism of

dimethyl terephthalate to terephthalic acid (D'A Heck and Kluwe, 1980). The LOAEL for this effect would appear to be 2500 ppm in the diet. This dietary dosage in rats is equivalent to 125 mg/kg/day, assuming that they consume food at a rate of 5% of their body weight/day (i.e., 2500 ppm x 0.05 = 125). Rats, rather than mice, are used because mice consume food equivalent to a greater percentage (13%) of their body weight/day.

A NOAEL of 4 mg/kg/day is obtained from the inhalation study of Krasavage et al. (1973). While some possible irritant effects (i.e., blinking, preening and nose rubbing) were observed at this inhalation dosage, comparable human occupational exposures would only occur at 20 times the TLV for respirable nuisance dust. This level is not used to derive an ADI because it resulted in local irritation from short-term exposure.

Using the chronic toxicity data from NCI (1979), a human ADI of 8.75 mg/man/day is obtained by dividing 125 mg/kg/day by 1000 and multiplying by the average weight of a human (70 kg). An uncertainty factor of 1000 is used to convert from a LOAEL to a NOAEL (10x), to extrapolate from animals to humans (10x) and to protect for the most sensitive humans (10x).

No data regarding the physical and chemical properties, pharmacokinetics, carcinogenicity, mutagenicity, teratogenicity and acute or chronic toxicity of methyl terephthalate were located in the available literature. It is an intermediate in the synthesis of dimethyl terephthalate and may also be an intermediate in mammalian metabolism of dimethyl terephthalate to terephthalic acid. The available information is, however, inadequate for predicting whether the toxicity of methyl terephthalate would be similar to that of dimethyl terephthalate.

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